Genetic draft, selective interference, and population genetics of rapid adaptation

Richard A. Neher

Max Planck Institute for Developmental Biology, Tübingen, 72070, Germany.
richard.neher@tuebingen.mpg.de

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To learn about the past from a sample of genomic sequences, one needs to understand how evolutionary processes shape genetic diversity. Most population genetic inference is based on frameworks assuming adaptive evolution is rare. But if positive selection operates on many loci simultaneously, as has recently been suggested for many species including animals such as flies, a different approach is necessary. In this review, I discuss recent progress in characterizing and understanding evolution in rapidly adapting populations where random associations of mutations with genetic backgrounds of different fitness, i.e., genetic draft, dominate over genetic drift. As a result, neutral genetic diversity depends weakly on population size, but strongly on the rate of adaptation or more generally the variance in fitness. Coalescent processes with multiple mergers, rather than Kingman's coalescent, are appropriate genealogical models for rapidly adapting populations with important implications for population genetic inference.

Contents

I. INTRODUCTION

Neutral diffusion or coalescent models (Kimura, 1964; Kingman, 1982) predict that genetic diversity at unconstrained sites is proportional to the (effective) population size N – for a simple reason: Two randomly chosen individuals have a common parent with a probability of order $1/N$ and the first common ancestor of two individuals lived of order N generations ago. Forward in time, this neutral coalescence corresponds to *genetic drift*. However, the observed correlation between genetic diversity and population size is rather weak (Leffler *et al.*, 2012; Lewontin, 1974), implying that processes other than genetic drift dominate coalescence in large populations. This notion is reinforced by the observation that pesticide resistance in insects can evolve independently on multiple genetic backgrounds (Karasov *et al.*, 2010; Labbé *et al.*, 2007) and can involve several adaptive steps in rapid succession (Schmidt *et al.*, 2010). This high mutational input suggests that the short-term effective population size of *D. melanogaster* is greater than 10^9 and conventional genetic drift should be negligible. Possible forces that accelerate coalescence and

reduce diversity are *purifying* and *positive* selection. Historically, the effects of purifying selection have received most attention (reviewed by Charlesworth (2012)) and my focus here will be on the role of positive selection.

A selective sweep reduces nearby polymorphims through *hitch-hiking*. Polymorphisms linked to the sweeping allele are brought to higher frequency, while others are driven out (Maynard Smith and Haigh, 1974). Linked selection not only reduces diversity, but also slows down adaptation in other regions of the genome – an effect known as Hill-Robertson interference (Hill and Robertson, 1966). Hill-Roberston interference has been intensively studied in two locus models (Barton, 1994) where the effect is quite intuitive: two linked beneficial mutations arising in different individuals compete and the probability that both mutations fix increases with the recombination rate between the loci. Pervasive selection, however, requires many-locus-models. Here, I will review recent progress in understanding how selection at many loci limits adaptation and shapes genetic diversity. Linked selection is most pronounced in asexual organisms. The theory of asexual evolution is partly motivated by evolution experiments with microbes, which have provided us with detailed information about the spectrum of adaptive molecular changes and their dynamics. I will then turn to facultatively sexual organisms which include many important human pathogens such as HIV and influenza as well as some plants and nematodes. Finally, I will discuss obligately sexual organisms, where the effect of linked selection is dominated by nearby loci on the chromosome.

The common aspect of all these models is the source of stochastic fluctuations: random associations with backgrounds of different fitness. In contrast to genetic drift, such associations persist for many generations, which amplifies their effect. In analogy to genetic drift, the fluctuations in allele frequencies through linked selection have been termed *genetic draft* (Gillespie, 2000). The (census) population size determines how readily adaptive mutations and combinations thereof are discovered but has little influence on coalescent properties and genetic diversity. Instead, selection determines genetic diversity and sets the time scale of coalescence. The latter should not be rebranded as N_e as this suggests that a rescaled neutral model is an accurate description of reality. In fact, many features are qualitatively different. Negligible drift does not imply that selection is efficient and only beneficial mutations matter. On the contrary, deleterious mutations can reach high frequency through linkage to favorable backgrounds and the dynamics of genotype frequencies in the population remains very stochastic. Genealogies of samples from populations governed by draft do not follow the standard binary coalescent process. Instead coalescent processes allowing for multiple mergers seem to be appropriate approximations which capture the large and anomalous fluctuations associated with selection. Those coalescent models thus form the basis for a *population genetics of rapid adaptation* and serve as null-models to analyze data when Kingman's coalescent is inappropriate. To illustrate clonal interference, draft, and genealogies in presence of selection, this review is accompanied by a collection of scripts based on FFPopSim (Zanini and Neher, 2012) at webdav.tuebingen.mpg.de/interference.

II. ADAPTATION OF LARGE AND DIVERSE ASEXUAL POPULATIONS

Evolution experiments (reviewed in Burke (2012); Kawecki *et al.* (2012)) have demonstrated that adaptive evolution is ubiquitous among microbes. Experiments with RNA viruses have shown that the rate of adaptation increases only slowly with the population size (Miralles *et al.*, 1999; de Visser *et al.*, 1999), suggesting that adaptation is limited by competition between different mutations and not by the availability of beneficial mutations. The competition between clones, also known as *clonal interference*, was directly observed in *E. coli* populations using fluorescent markers (Hegreness *et al.*, 2006). Similar observations have been made in Rich Lenski's experiments in which *E. coli* populations were followed for more that 50000 generations (Barrick *et al.*, 2009). A different experiment selecting > 100 *E. coli* populations for heat tolerance has shown that there are 1000s of sites available for adaptive substitutions, that there is extensive parallelism among lines in the genes and pathways bearing mutations, and that mutations frequently interact epistatically (Tenaillon *et al.*, 2012). By following the frequencies of microsatellite markers in populations of *E. coli*, Perfeito *et al.* (2007) estimated the beneficial mutation rate to be $U_b \approx 10^{-5}$ per genome and generation with average effects of about 1%. Similarly, it has been shown that beneficial mutations are readily available in yeast and compete with each other in the population for fixation (Desai *et al.*, 2007; Kao and Sherlock, 2008; Lang *et al.*, 2011). At any given instant, the population is thus characterized by a large number of segregating clones giving rise to a broad fitness distribution (Desai *et al.*, 2007). The fate of a novel mutation is mainly determined by the genetic background it arises on (Lang *et al.*, 2011). Similar rapid adaptation and competition is observed in the global populations of influenza, which experience several adaptive substitutions per year (Bhatt *et al.*, 2011; Smith *et al.*, 2004; Strelkowa and Lässig, 2012), mainly driven by immune responses of the host. In summary, evolution of asexual microbes does not seem to be limited by finding the necessary single point mutations, but rather by overcoming clonal interference and combining multiple mutations.

These observations have triggered intense theoretical research on clonal interference and adaptation in asexuals. In the models studied, rare events, e.g. the fittest individual acquiring additional mutations, dramatically affect the future dynamics. Intuition is a poor guide in such situations and careful mathematical treatment is warranted. Nevertheless,

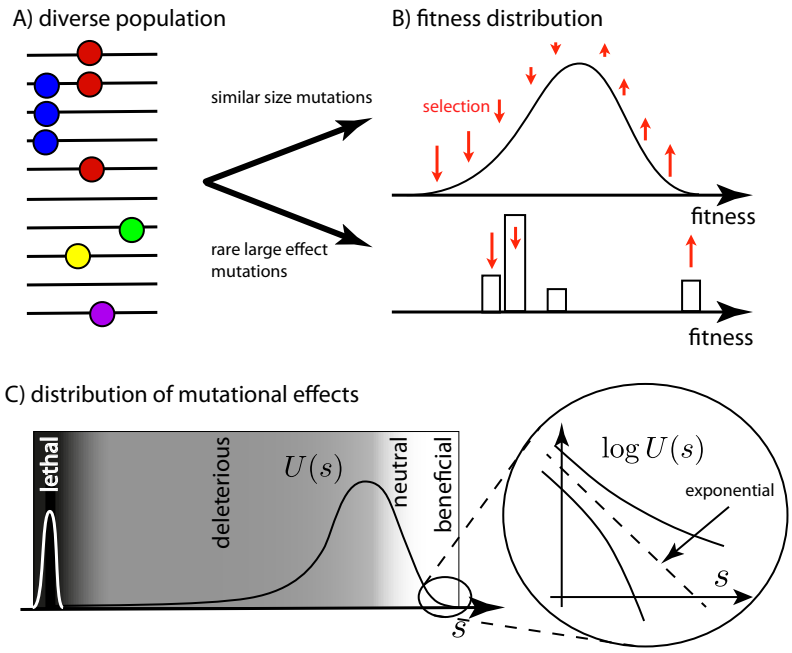

FIG. 1 Fitness and mutational effect distributions. (a) A genetically diverse population will typically harbor variation in fitness. If many mutations have comparable effects on fitness, the resulting fitness distribution is smooth and roughly normal (part b, top). If a small number of large effect mutation exists, the distribution is multi-modal (part b, bottom). Mutational effects across the genome are believed to follow a distribution roughly like the one sketched in panel (c). A small fraction of mutations are beneficial, the majority are neutral or deleterious, and some are lethal. The integral over $U(s)$ is the total mutation rate U. In models of adaptive evolution, the high fitness tail of $U(s)$, shown into in the inset, is the most important part. If it falls off faster than exponentially, the fitness distribution tends to be smooth. Otherwise, the distribution is often dominated by a few large effect mutations.

it is often possible to rationalize the results in a simple and intuitive way with hindsight, and I will try to present the important aspects in accessible form.

Our discussion assumes that fitness is a unique function of the genotype. Thereby, we ignore the possibility of frequency-dependent selection. A diverse population with many different genotypes can then be summarized by its distribution along this fitness-axis; see Fig. 1A&B. Fitness distributions are shaped by a balance between injection of variation via mutation and the removal of poorly adapted variants. Most mutations have detrimental effects on fitness, while only a small minority of mutations is beneficial. The distribution of mutational effects in RNA virus has been estimated by mutagenesis (Lalić *et al.*, 2011; Sanjuán *et al.*, 2004). Roughly half of random mutations are effectively lethal, while 4% were found to be beneficial in this experiment. A distribution of mutational effects, $U(s)$, is sketched in Fig. 1C. General properties of $U(s)$ are largely unknown and will depend on the environment.

Deleterious mutations rarely reach high frequencies but are numerous, while beneficial mutations are rare but amplified by selection. But in order to spread and fix, a beneficial mutation has to arise on an already fit genetic background or have a sufficiently large effect on fitness to get ahead of everybody else. Two lines of theoretical works have put emphasis either on the large effect mutations (clonal interference theory) or "coalitions" of multiple mutations of similar effect. Both approaches, sketched in Fig. 2 are good approximations depending on the distribution of fitness effects.

A. Clonal Interference

Consider a homogeneous population in which mutations with effect on fitness between s and $s + ds$ arise with rate $U(s)ds$ as sketched in Fig. 1C. In a large population many beneficial mutations arise every generation. In order to fix, a beneficial mutation has to outcompete all others; see Fig. 2A. In other words, a mutation fixes only if no mutation with a larger effect arises before it has reached high frequencies in the population. This is the essence of clonal interference theory by Gerrish and Lenski (1998). The Gerrish-Lenski theory of clonal interference is an

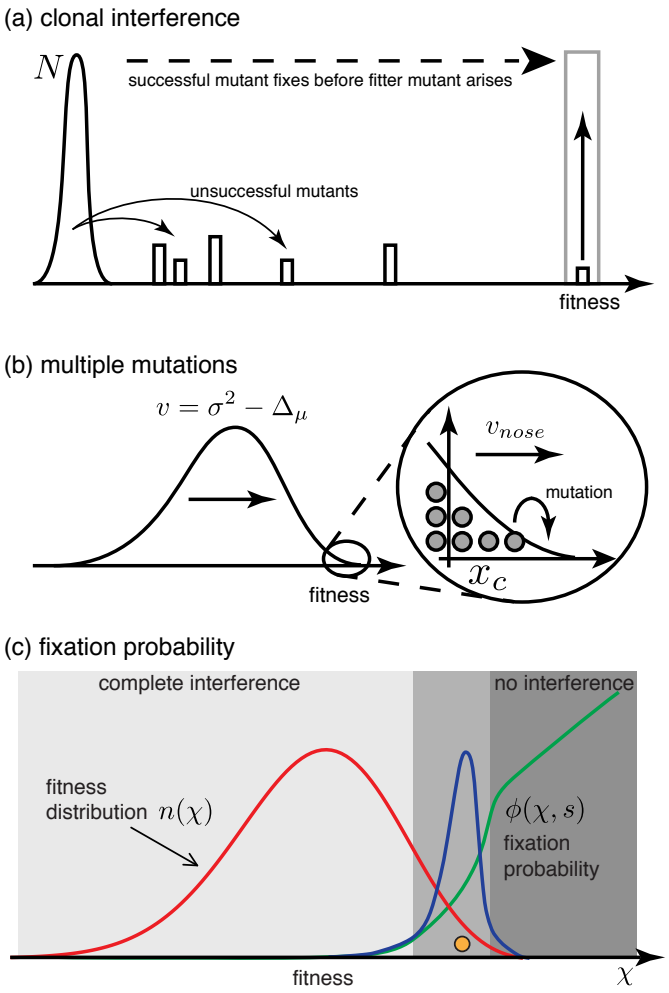

FIG. 2 Adaptation in asexual populations. (a) If the distribution of beneficial mutation has a long tail, the population consists of a small number of large clones and only the mutations with the largest effects have a chance of fixing. (b) If many mutations of similar effect contribute to fitness diversity, the bulk of the fitness distribution can be described by a smooth function that is roughly Gaussian in shape. There exists a fittest genotype in the population with no individuals to its right. Only mutations close to this high fitness "nose" have an appreciable chance of fixing. The stochastic dynamics at the nose determines the evolution of the entire population and the speed of the entire population, v, has to match the speed of the nose, v_{nose}, in a quasi-steady state. The fixation probability $\phi(\chi, s)$ of a mutation with effect s increases with increasing background fitness as sketched in panel (c). A mutant in the bulk of the fitness distribution has essentially zero chance of taking over the population since many fitter individuals exist. In the opposite case when the mutant is the fittest in the population, $\phi(\chi, s)$ is proportional to $\chi + s$ as we would expect in the absence of interference. Since there are very few individuals with very high fitness, most mutations that fix come from a narrow region (light grey) where the product of $n(\chi)$ and $\phi(\chi, s)$, sketched in blue, peaks. Note that χ is Malthusian or log-fitness. Scripts to illustrate interference and fixation can be found in the online supplement.

approximation since it ignores the possibility that two or more mutations with moderate effects combine to outcompete a large effect mutation – a process I will discuss below. Its accuracy depends on the functional form of $U(s)$ and the population size (Park and Krug, 2007). One central prediction of clonal interference is that the rate of adaptation increases only slowly with the population size N and the beneficial mutation rate U_b. This is a consequence of the fact that the probability that a particular mutation is successful decreases with NU_b since there are more mutations competing. This basic prediction has been confirmed in evolution experiments with virus (Miralles *et al.*, 1999, 2000; de Visser *et al.*, 1999). How the rate of adaptation depends on N and U_b is sensitive to the distribution of fitness effects $U(s)$. Generically, one finds that the rate of adaptation is $\propto (\log NU_b)^\alpha$, where α depends on the properties of $U(s)$ (Park *et al.*, 2010).

Clonal interference theory places all the emphasis on the mutation with the largest effect and ignores variation in genetic background or equivalently the possibility that multiple mutations accumulate in one lineage. It is therefore

expected to work if the distribution of effect sizes has a long tail allowing for mutations of widely different sizes. It fails if most mutations have similar effects on fitness. A careful discussion of the theory of clonal interference and its limitations can be found in Park *et al.* (2010).

B. Genetic background and multiple mutations

If most beneficial mutations have similar effects, a lineage cannot fix by acquiring a mutation with very large effect but has to accumulate more beneficial mutations than the competing lineages. If population sizes and mutation rates are large enough that many mutations segregate, the distribution $n(x,t)$ of fitness x in the population is roughly Gaussian, see Fig. 2B, and the problem becomes tractable (Desai and Fisher, 2007; Rouzine *et al.*, 2003; Tsimring *et al.*, 1996). More precisely, $n(x,t)$ is governed by the deterministic equation

$$\frac{d}{dt}n(x,t) = (x-\bar{x})n(x,t) + \int U(s)[n(x-s,t) - n(x,t)]\,ds \tag{1}$$

where $(x-\bar{x})n(x,t)$ accounts for amplification by selection of individuals fitter than the fitness mean $\bar{x}$ and elimination of the less fit ones. The second term accounts for mutations that move individuals from $x-s$ to x at rate $U(s)$. Integrating this equation over the fitness x yields Fisher's "Fundamental Theorem of Natural Selection", which states that the rate of increase in mean fitness is

$$\frac{d}{dt}\bar{x} = v = \sigma^2 - \Delta_\mu \tag{2}$$

where σ^2 is the variance in fitness and Δ_μ is the average mutation load a genome accumulates in one generation. A steadily moving mean fitness $\bar{x} = vt$ suggests a traveling wave solution of the form $n(x,t) = n(\chi)$ where $\chi = x - \bar{x}$ is the fitness relative to the mean. Eq. (2) is analogous to the breeder's equation that links the response to selection to additive variances and co-variances. In quantitative genetics, the trait variances are determined empirically and often assumed constant, while we will try to understand how σ^2 is determined by a balance between selection and mutation.

To determine the average v, we need an additional relation between v and the mutational input. To this end, it is important to realize that the population is thinning out at higher and higher fitness and only very few individuals are expected to be present above some χ_c as sketched in Fig. 2B. The dynamics of this high fitness "nose" is very stochastic and not accurately described by Eq. (1). However, the nose is the most important part where most successful mutations arise. There have been two strategies to account for the stochastic effects and derive an additional relation for the velocity. (i) The average velocity, v_{nose}, of the nose is determined by a detailed study of the stochastic dynamics of the nose. At steady state, this velocity has to equal the average velocity of the mean fitness given by Eq. (2), which produces the additional relation required to determine v (Brunet *et al.*, 2008; Cohen *et al.*, 2005a; Desai and Fisher, 2007; Goyal *et al.*, 2012; Rouzine *et al.*, 2003; Tsimring *et al.*, 1996). (ii) Alternatively, assuming additivity of mutations, v has to equal the average rate at which fitness increases due to fixed mutations (Good *et al.*, 2012; Neher *et al.*, 2010) (see (Hallatschek, 2011) for a related idea). I will largely focus on this latter approach, as it generalizes to sexual populations below. In essence, we need to calculate the probability of fixation $\Phi(s,v)$ of mutations with effect size s that arise in random individuals in the population. Φ depends on v and implicitly on the traveling fitness distribution $n(x-vt)$. Using this notation, we can express v as the sum of effects of mutations that fix per unit time:

$$v = \frac{d}{dt}\bar{x} = N\int U(s)\Phi(s,v)s\,ds \tag{3}$$

Note that the mutational input is proportional to the census population size N. To solve Eq. (3), we first have to calculate the fixation probability $\Phi(s,v)$, which in turn is a weighted average of the fixation probability, $\phi(\chi,s)$, given the mutation appears on a genetic background with relative fitness χ. The latter can be approximated by branching processes (Good *et al.*, 2012; Neher *et al.*, 2010). A detailed derivation of $\phi(\chi,s)$ is given in the supplement of Good *et al.* (2012), while the subtleties associated with approximations are discussed in Fisher (2013). The qualitative features of $\phi(\chi,s)$ are sketched in Fig. 2C.

The product $n(\chi)\phi(\chi,s)$ describes the distribution of backgrounds on which successful mutations arise. This distribution is often narrowly peaked right below the high fitness nose (see Fig. 2C). Mutations on backgrounds with lower fitness are doomed, while there are very few individuals with even higher background fitness. The larger s, the broader this region is.

To determine the rate of adaptation, one has to substitute the results for $\Phi(s,v)$ into Eq. (3) and solve for v (Desai and Fisher, 2007; Good *et al.*, 2012). A general consequence of the form of the self-consistency condition Eq. (3) is that

if Φ is weakly dependent on v, we will find v proportional to N. In this case the speed of evolution is proportional to the mutational input. With increasing fitness variance, σ^2, the genetic background fitness starts to influence fixation probabilities, such that eventually v increases only slowly with N. For models in which beneficial mutations of fixed effect s arise at rate U_b, the rate of adaptation in large populations is given by

$$v \propto \begin{cases} s^2 \frac{\log Ns}{(\log U_b/s)^2} & s \gg U_b \\ (U_b s^2)^{\frac{2}{3}} (\log ND^{1/3})^{1/3} & s \ll U_b \end{cases} \tag{4}$$

(Cohen *et al.*, 2005a; Desai and Fisher, 2007). The above has assumed that s is constant, but these expressions hold for more general models with a short-tailed distribution $U(s)$ with suitably defined effective U_b and s (Good *et al.*, 2012).

Synthesis Clonal interference and multiple mutation models both predict diminishing returns as the population increases, but the underlying dynamics are rather different. In the clonal interference picture, population take-overs are driven by single mutations and the genetic background on which they occur is largely irrelevant ($\phi(\chi, s)$ depends little on χ). The mutations that are successful, however, have the very largest effects. In the multiple mutation regime, the effect of the mutations is not that crucial, but they have to occur in very fit individuals to be successful ($\phi(\chi, s)$ increases rapidly with χ). In both models, the speed of adaptation continues to increase slowly with the population size and there is no hard "speed limit". Distinguishing a speed limit from diminishing returns in experiments is hard (Miralles *et al.*, 2000; de Visser *et al.*, 1999).

Whether one or the other picture is more appropriate depends on the distribution of available mutations $U(s)$. If $U(s)$ falls off faster than exponential, adaptation occurs via many small steps (Desai and Fisher, 2007; Good *et al.*, 2012); if the distribution is broader, the clonal interference picture is a reasonable approximation (Park and Krug, 2007; Park *et al.*, 2010). The borderline case of an exponential fitness distribution has been investigated more closely, finding that large effect mutations on a pretty good background make the dominant contributions (Good *et al.*, 2012; Schiffels *et al.*, 2011), i.e., a little bit of both.

Empirical observations favor this intermediate situation. Influenza evolution has been analyzed in great detail and is was found that a few rather than a single mutation drive the fixation of a particular strain (Strelkowa and Lässig, 2012). Similarly, evolution experiments suggest that the genetic background is important, but a moderate number of large effect mutations account for most of the observed adaptation (Lang *et al.*, 2011).

Note the somewhat unintuitive dependence of v on parameters in Eq. (4). Instead of the mutational input NU_b and s, v depends on Ns and U_b/s for $U_b \ll s$. In large populations, the dominant time scale of population turnover is goverened by selection and is of order s^{-1}. Ns and U_b/s measure the strength of reproduction noise (drift) and mutations relative to s^{-1}, respectively (see Neher and Shraiman (2012) for a discussion of this issue in the context of deleterious mutations). In large populations, the infinite sites model starts to break down and the same mutations can occur independently in several lineages limiting interference (Bollback and Huelsenbeck, 2007; Kim and Orr, 2005).

III. EVOLUTION OF FACULTATIVELY SEXUAL POPULATIONS

Competition between beneficial mutations in asexuals results in a slow (logarithmic) growth of the speed of adaptation with the population size N (Eq. (4)). How does gradually increasing the outcrossing rate alleviate this competition? The associated advantages of sex and recombination have been studied extensively (Charlesworth, 1993; Crow and Kimura, 1965; Fisher, 1930; Muller, 1932; Rice and Chippindale, 2001). It is instructive to consider facultatively sexual organisms that outcross at rate r, and in the event of outcrossing have many independently segregating loci. Facultatively sexual species are common among RNA viruses, yeasts, nematodes, and plants.

Most of our theoretical understanding of evolution in large facultatively mating populations comes from models similar to those introduced above for asexual populations. In addition to mutation, we have to introduce a term that describes how an allele can move from one genetic background to another by recombination; see Fig. 3A. Given the fitness values of the two parents χ_1 and χ_2 and assuming many independently segregating loci, the offspring fitness χ is symmetrically distributed around the mid-parent value with half the population variance; see illustration in Fig. 3A and (Bulmer, 1980; Turelli and Barton, 1994). To understand the process of fixation in such a population, the following is a useful intuition: An outcrossing event places a beneficial mutation onto a novel genotype, which is amplified by selection into a clone whose size grows rapidly with the fitness of the founder; see Fig. 3B. These clones are transient, since even an initially fit clone falls behind the increasing mean fitness. However, large clones produce many recombinant offspring (daughter clones), which greatly enhances the chance of fixation of mutations they carry. Since clone size increases rapidly with founder fitness, the fixation probability $\phi(\chi, s)$ is still a very steep function of

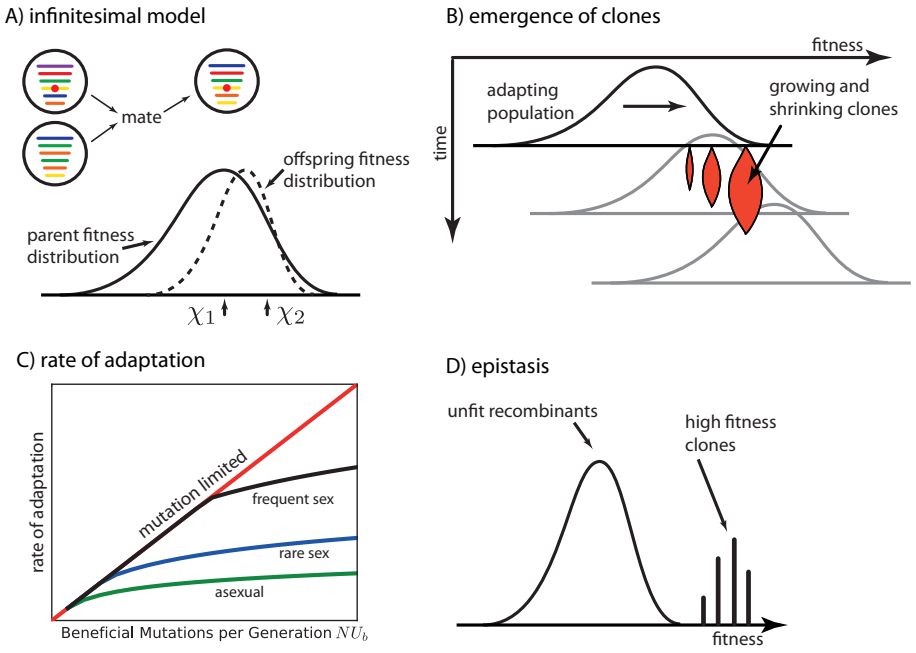

FIG. 3 A facultatively sexual lifecycle is common among many pathogens, plants, and some groups of animals. (a) If many loci segregate independently, recombination can be modeled by the infinitesimal model. Given two parents with fitness χ_1 and χ_2 sampled from the parental distribution with variance σ^2, offspring fitness is symmetrically distributed around the parental mean with variance $\sigma^2/2$. A mutation, indicated as a red dot in the sketch, can thereby hop from an individual with one background fitness to a very different one. (b) If the outcrossing rate is lower than the fitness of some individuals, clones, indicated in red, can grow at rate $\chi - r$. As the population adapts, the growth rate of the clones is reduced, eventually goes negative and the clone disappears. The beneficial mutation, however, persists on other backgrounds. In small populations, the rate of adaptation increases linearly with the population size as sketched in panel (c). For each outcrossing rate, there is a point beyond which interference starts to be important. (d) Epistasis causes condensation of the population into a small number of very fit genotypes. Crosses between these genotypes result in unfit individuals. In the absence of forces that stabilize different clones, one clone will rapidly take over if $\chi > r$. Scripts illustrating evolution of faculatively sexual populations can be found in the online supplement.

the background fitness and qualitatively similar to the asexual case (Fig. 2C). With increasing outcrossing rate, the fitness window from which successful clones originate becomes broader and broader.

If outcrossing rates are large enough that genotypes are disassembled by recombination faster than selection can amplify them, $\phi(\chi, s)$ is essentially flat and the genetic background does not matter much. This transition was examined by Neher *et al.* (2010):

$$v \approx \begin{cases} \frac{2r^2 \log(NU_b)}{(\log r/s)^2} & r \ll \sqrt{NU_b s^2} \\ NU_b s^2 & r \geq \sqrt{NU_b s^2} \end{cases} . \tag{5}$$

The essence of this result is that adaptation is limited by recombination whenever r is smaller than the standard deviation in fitness in the absence of interference. In this regime, v depends weakly on N, but increases rapidly with r. This behavior is sketched in Fig. 3C. Similar results can be found in Weissman and Barton (2012). The above analysis assumed that recombination is rare, but still frequent enough to ensure that mutations that rise to high frequencies are essentially in linkage equilibrium. This requires $r \gg s$. Rouzine and Coffin (2005, 2010) studied the selection on standing variation at intermediate and low recombination rates. Adaptation in presence of horizontal gene transfer was investigated by Cohen *et al.* (2005b), Wylie *et al.* (2010), and Neher *et al.* (2010).

In contrast to asexual evolution, epistasis can dramatically affect the evolutionary dynamics in sexual populations. Epistasis implies that the effect of mutations depends on the state at other loci in the genome. In the absence of sex, the only quantity that matters is the distribution of available mutations, $U(s)$. The precise nature of epistasis is not crucial. In sexual populations, however, epistasis can affect the evolutionary dynamics dramatically: When different individuals mix their genomes, it matters whether mutations acquired in different lineages are compatible.

Since selection favors well adapted combinations of alleles, recombination is expected to be on average disruptive and recombinant offspring have on average lower fitness than their parents (the so-called "recombination load"). This competition between selection for good genotypes and recombination can result in a condensation of the population into fit clones; see Fig. 3D, Neher and Shraiman (2009) and Neher *et al.* (2013).

IV. SELECTIVE INTERFERENCE IN OBLIGATELY SEXUAL ORGANISMS

Selective interference has historically received most attention in obligately sexual organisms most relevant to crop and animal breeding. Artificial selection has been performed by farmers and breeders for thousands of years with remarkable success (Hill and Kirkpatrick, 2010). Evolution experiments with diverse species, including chicken, mice and Drosophila, have shown that standing variation at a large number of loci responds to diverse selection pressures (Burke *et al.*, 2010; Chan *et al.*, 2012; Johansson *et al.*, 2010; Turner *et al.*, 2011; Zhou *et al.*, 2011); see Burke (2012) for a recent review. In obligately sexual populations, distant loci can respond independently to selection and remain in approximate linkage equilibrium. The frequencies of different alleles change according to their effect on fitness averaged over all possible fitness backgrounds in the population. Small deviations from linkage equilibrium can be accounted for perturbatively using the so-called Quasi-Linkage Equilibrium (QLE) approximation (Barton and Turelli, 1991; Kimura, 1965; Neher and Shraiman, 2011a).

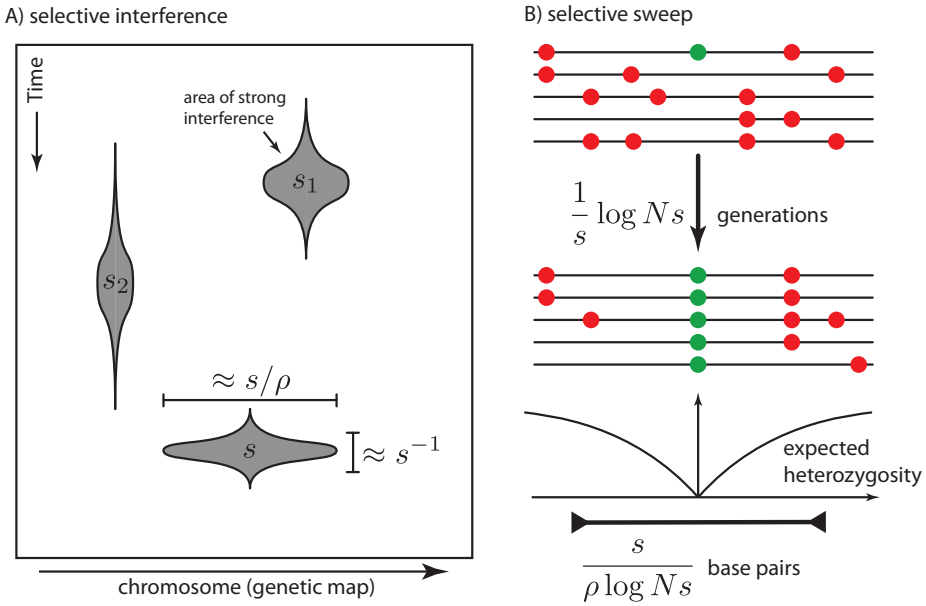

FIG. 4 Interference in obligately sexual populations. Panel (a) sketches the interference effects of selective sweeps through time (vertical axis) and along the genome (horizontal axis). A sweeping mutation with selection coefficient s interferes with other mutation in a region of width s/ρ over a time s^{-1}, where ρ is the crossover rate per base. The extent of interference is sketched by grey bulges, each of which corresponds to a mutation that fixed. Interference starts to be important when the bulges overlap. Since the area of the bulges, roughly "height×width", is approximately independent of s, interference depends on ρ and the rate of sweeps rather than the effect size. The rate of adaptation is therefore primarily a function of the maplength R. (b) A selective sweep reduces neutral genetic variation in a region of width $s/(\rho \log(Ns))$. The effect of sweeps on neutral diversity is explored in online supplement

This approximate independence, however, does not hold for loci that are tightly linked. Hill and Robertson (1966) observed that interference between linked competing loci can slow down the response to selection – an effect now termed *Hill-Robertson interference* (Felsenstein, 1974). Felsenstein realized that interference is not restricted to competing beneficial mutations but that linked deleterious mutations also impede fixation of beneficial mutations (see background selection below). The term Hill-Robertson interference is now used for any reduction in the efficacy of selection caused by linked fitness variation. A deeper understanding of selective interference was gained in the 1990ies (Barton, 1994, 1995b). The key insight of Barton was to calculate the fate of a novel mutation considering all possible genetic backgrounds on which it can arise and summing over all possible trajectories it can take through

the population. For a small number of loci, the equations describing the probability of fixation can be integrated explicitly.

Weakly-linked sweeps cause a cumulative reduction of the fixation probability at a focal site that is roughly given by the ratio of additive variance in fitness and the squared degree of linkage (Barton, 1995b; Santiago and Caballero, 1998). Barton (1994) further identified a critical rate of strong selective sweeps that effectively prevents the fixation of mutations with an advantage smaller than s_c. If sweeps are too frequent, the weakly selected mutation has little chance of spreading before its frequency is reduced again by the next strong sweep.

At short distances, selective sweeps impede each other's fixation more strongly. This interference is limited to a time interval of order s^{-1} generations where one of the sweeping mutations is at intermediate frequencies. During this time, a new beneficial mutation will often fall onto the wildtype background and is lost again if it is not rapidly recombined onto the competing sweep. The latter is likely only if it is further than s/ρ nucleotides away from the competing sweep, where ρ is the crossover rate per basepair (Barton, 1994). In other words, a sweeping mutation with effect s prevents other sweeps in a region of width s/ρ, and occupies this chromosomal "real estate" for a time s^{-1}; see Fig. 4A (Weissman and Barton, 2012). Hence strong sweeps briefly interfere with other sweeps in a large region, while weak sweeps affect a narrow region for a longer time. The amount of interference is therefore roughly independent of the strength of the sweeps, and the total number of sweeps per unit time is limited by the map-length $R = \int \rho(y)\, dy$, where the integral is over the entire genome and $\rho(y)$ is the local crossover rate. Larger populations can squeeze slightly more sweeps into R (Weissman and Barton, 2012). In most obligately sexual organisms, sweeps rarely cover more than a few percent of the total map length such that recombination is not limiting adaptation unless sweeps cluster in certain regions (Sella *et al.*, 2009). However, as I will discuss below, even rare selective sweeps have dramatic effects on neutral diversity.

V. GENETIC DIVERSITY, DRAFT, AND COALESCENCE

Interference between selected mutations reduces the fixation probability of beneficial mutations, slows adaptation, and weakens purifying selection. These effects are very important, but hard to observe since significant adaptation often takes longer than our window of observation. Typically, data consists of a sample of sequences from a population. These sequences differ by single nucleotide polymorphisms, insertions, or deletions, and we rarely know the effect of these differences on the organism's fitness.

From a sequence sample of this sort, the genealogy of the population is reconstructed and compared to models of evolution – in most cases a neutral model governed by Kingman's coalescent (Kingman, 1982). From this comparison we hope to learn about evolutionary processes. However, linked selection, be it in asexual organisms, facultatively sexuals, or obligately sexuals, has dramatic effects on the genealogies. Substantial effects on neutral diversity are observed at rates of sweeps that do not yet cause strong interference between selected loci for the simple reason that neutral alleles segregate for longer times (Weissman and Barton, 2012).

A. Genetic draft in obligately sexual populations

Selective sweeps have strong effects on linked neutral diversity and genealogies (Barton, 1998; Barton and Etheridge, 2004; Kaplan *et al.*, 1989; Maynard Smith and Haigh, 1974; Stephan *et al.*, 1992; Wiehe and Stephan, 1993). A sweeping mutation takes about $t_{sw} \approx s^{-1} \log Ns$ generations to rise to high frequency. Linked neutral variation is preserved only when substantial recombination happens during this time. Given a crossover rate ρ per base, recombination will separate the sweep from a locus at distance l with probability $r = \rho l$ per generation (assuming $r \ll 1$). Hence a sweep leaves a dip of width $l = (\rho t_{sw})^{-1} \approx s/(\rho \log Ns)$ in the neutral diversity (see Fig. 4B). Within this region, selection causes massive and rapid coalescence and only a fraction of the lineages continue into the ancestral population (see Fig. 5A). This effect has been further investigated by Durrett and Schweinsberg (2005), who showed that the effect of recurrent selective sweeps is well approximated by a coalescent process that allows for multiple mergers: each sweep forces the almost simultaneous coalescence of a large number of lineages (a fraction $e^{-rt_{sw}}$). Similar arguments had been made previously by Gillespie (2000), who called the stochastic force responsible for coalescence *genetic draft*. Coop and Ralph (2012) extended the analysis of Durret and Schweinsberg partial sweeps that could be common in structured populations, with over-dominance, or frequency dependent selection.

The rapid coalescence of multiple lineages is unexpected in the standard neutral coalescent (a merger of p lineages occurs with probability $\propto N^{-p}$). In coalescence induced by a selective sweep, however, multiple mergers are common and dramatically change the statistical properties of genealogies. A burst of coalescence corresponds to a portion of the tree with almost star-like shape (Slatkin and Hudson, 1991). Alleles that arose before the burst are common, those after the burst rare. This causes a relative increase of rare alleles, as well as alleles very close to fixation (Braverman

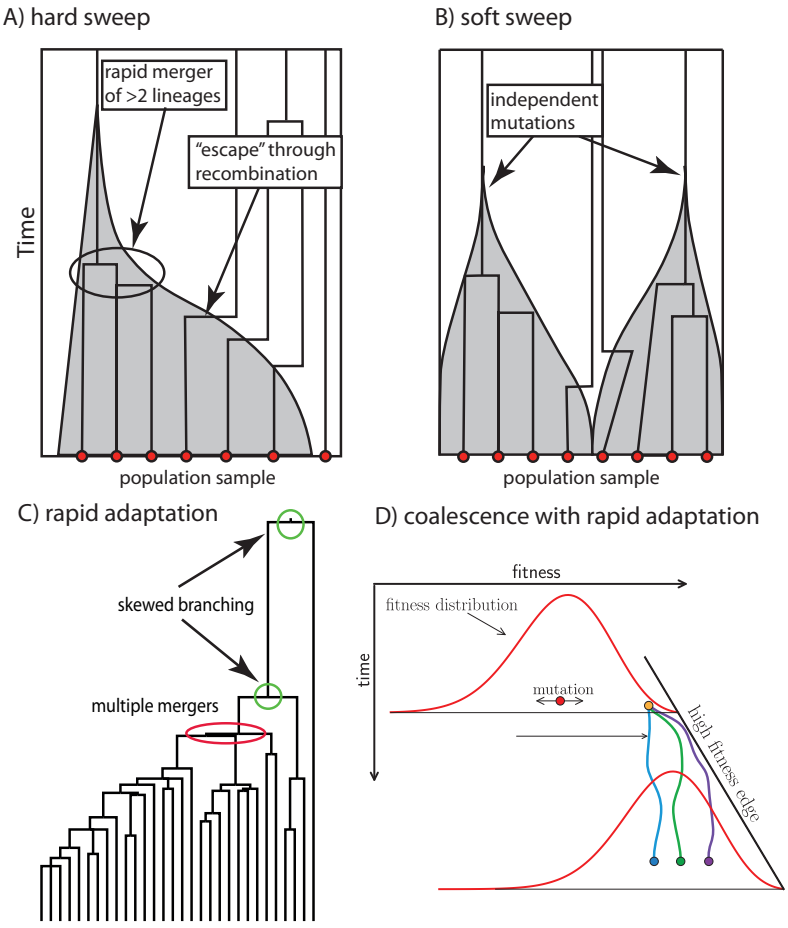

FIG. 5 Coalescence driven by selection. (a) A selective sweep (grey region) causes rapid coalescence of lineages at a nearby locus. Each sweep causes a fraction of lineages to merge, while the remainder recombines onto an ancestral background. (b) Soft sweeps refer to a scenario where single mutations arise multiple times independently in response to environmental change. This is expected as soon as the product of N and the per site mutation rate exceeds one and can result in multiple bursts of coalescence almost at the same time. (c) A genealogical tree drawn from a simulation of a model of rapidly adapting asexual organisms. Coalescence often occurs in bursts. Furthermore, branching is often uneven. At many branchings in this "ladderized" tree, most individuals descend from the left branch. Those are well known features of multiple merger coalescence processes such as the Bolthausen-Sznitman coalescent. (d) Coalescence and fitness classes. Most population samples consists of individual from the center of the fitness distribution, while their distant ancestors were among the fittest. In large populations, most coalescence happens in the high fitness nose and the time until ancestral lineages "arrive" in the nose corresponds to long terminal branches (compare panel c). How genealogies depend on selection can be studied using simulations, see online supplement.

et al., 1995; Fay and Wu, 2000; Gillespie, 2000).

The degree to which linked selective sweeps reduce genetic diversity depends primarily on the rate of sweeps per map length (Weissman and Barton, 2012). In accord with this expectation, it is found that diversity increases with recombination rate and decreases with the density of functional sites (Begun *et al.*, 2007; Shapiro *et al.*, 2007). In addition to occasional selective sweeps, genetic diversity and the degree of adaptation can be strongly affected by a large number of weakly selected sites, e.g. weakly deleterious mutations, that generate a broad fitness distribution (McVean and Charlesworth, 2000).

B. Soft sweeps

Soft sweeps refer to events when a selective sweep originates from multiple genomic backgrounds (Hermisson and Pennings, 2005; Pennings and Hermisson, 2006), either because the favored allele arose independently multiple times

or because it has been segregating for a long time prior to a environmental change. Soft sweeps have recently been observed in pesticide resistance of Drosophila (Karasov *et al.*, 2010) and are a common phenomenon in viruses with high mutation rates.

A genealogy of individuals sampled after a soft sweep is illustrated in Fig. 5B. The majority of the individuals trace back to one of two or more ancestral haplotypes on which the selected mutation arose. Hence coalescence is again dominated by multiple merger events, except that several of those events happen almost simultaneously. This type of coalescent process has been described in Schweinsberg (2000).

Despite dramatic effects on genealogies, soft sweeps can be difficult to detect by standard methods that scan for selective sweeps. Those methods use local reductions in genetic diversity, which can be modest if the population traces back to several ancestral haplotypes. The number of ancestral haplotypes in a sample after a soft sweep depends on the product of N, the per-site mutations rate μ, and selection against the allele before the sweep (Pennings and Hermisson, 2006). To detect soft sweeps, methods are required that explicitly search for signatures of rapid coalescence into several lineages in linkage disequilibrium or haplotype patterns (Messer and Neher, 2012; Pennings and Hermisson, 2006).

C. The Bolthausen-Sznitman coalescent and rapidly adapting populations

Individual selective sweeps have an intuitive effect on genetic diversity, but what do genealogies look like when many mutations are competing in asexual or facultatively sexual populations? It has recently been argued that the genealogies of populations in many models of rapid adaptation are well described by coalescent processes with multiple mergers (Berestycki, 2009; Pitman, 1999). This was first discovered by Brunet *et al.* (2007), who studied a model where a population expands its range. The genealogies of individuals at the front are described by the Bolthausen-Sznitman coalescent, a special case of coalescent processes with multiple mergers. Recently, it has been shown that a similar coalescent process emerges in models of adaptation in panmictic populations (Desai *et al.*, 2012; Neher and Hallatschek, 2013).

Fig. 5C shows a tree sampled from a model of a rapidly adapting population. A typical sample from a rapidly adapting population will consist of individuals from the center of the fitness distribution. Their ancestors tend to be among the fittest in the population (Hermisson *et al.*, 2002; Rouzine and Coffin, 2007). Substantial coalescence happens only once the ancestral lineages have reached the high fitness tip, resulting in long terminal branches of the trees. Once in the tip, coalescence is driven by the competition of lineages against each other and happens in bursts whenever one lineage gets ahead of everybody else. These bursts correspond to the event that a large fraction of the population descends from one particular individual. These coalescent events have approximately the same statistics as neutral coalescent processes with very broad but non-heritable offspring distributions (Der *et al.*, 2011; Eldon and Wakeley, 2006; Schweinsberg, 2003).

In the case of rapidly adapting asexual populations, the effective distribution of the number n of offspring is given by $P(n) \sim n^{-2}$ which gives rise to the Bolthausen-Sznitman coalescent. This type of distribution seems to be universal to populations in which individual lineages are amplified while they diversify and is found in facultatively sexual populations (Neher and Shraiman, 2011b), asexual populations adapting by small steps, as well as populations in a dynamic balance between deleterious and beneficial mutations. Asymptotic features of the site frequency spectrum can be derived analytically (Berestycki, 2009; Desai *et al.*, 2012; Neher and Hallatschek, 2013). One finds that the frequency spectrum diverges as $f(\nu) \sim \nu^{-2}$ at low frequencies corresponding to many singletons. Furthermore, neutral alleles close to fixation are common with $f(\nu)$ diverging again as $\nu \to 1$. This relative excess of rare and very common alleles is a consequence multiple mergers which produce star-like sub-trees and the very asymmetric branching at nodes deep in the tree (compare Fig. 5C).

The time scale of coalescence, and with it the level of genetic diversity, is mostly determined by the strength of selection and only weakly increases with population size. Essentially, the average time to a common ancestor of two randomly chosen individuals is given by the time it takes until the fittest individuals dominate the population. In most models, this time depends only logarithmically on the population size N.

D. Background selection and genetic diversity

Background selection refers to the effect of purifying selection on linked loci, which is particularly important if linked regions are long. If deleterious mutations incur a fitness decrement of s and arise with genome wide rate U_d, a sufficiently large population settles in a state where the number of mutations in individuals follows a Poisson distribution with mean $\lambda = U_d/s$ (Haigh, 1978). Individuals loaded with many mutations are selected against, but continually produced by de novo mutations. All individuals in the population ultimately descent from individuals

carrying least deleterious mutations. Within this model, the least loaded class has size $N\exp(-U_d/s)$ and coalescence in this class is accelerated by $\exp(U_d/s)$ compared to a neutrally evolving population of size N (Charlesworth *et al.*, 1993). For large ratios U_d/s, the Poisson distribution of background fitness spans a large number of fitness classes and this heterogeneity substantially reduces the efficacy of selection (McVean and Charlesworth, 2000).

The effect of background selection is best appreciated in a genealogical picture. Genetic backgrounds sampled from the population tend to come from the center of the distribution. Since the deleterious mutations they carry were accumulated in the recent past, lineages "shed" mutations as we trace them back in time until they arrive in the mutation free class akin to Fig. 5D. This resulting genealogical process, a fitness class coalescent, has been described in Walczak *et al.* (2012). A recent study on the genetic diversity of whale lice (Seger *et al.*, 2010) suggests that purifying selection and frequent deleterious mutations can severely distort genealogies. O'Fallon *et al.* (2010) present methods for the analysis of sequence samples under purifying selection.

The fitness class coalescent is appropriate as long as Muller's ratchet does not yet click. More generally, fixation of deleterious mutations, adaptation, and environmental change will balance approximately. It has been shown that a small fraction of beneficial mutations can be sufficient to halt Muller's ratchet (Goyal *et al.*, 2012). In this dynamic balance between frequent deleterious and rare beneficial mutations, the genealogies tend to be similar to genealogies under rapid adaptation discussed above.

VI. CONCLUSIONS AND FUTURE DIRECTIONS

Contradicting neutral theory, genetic diversity correlates only weakly with population size (Leffler *et al.*, 2012), suggesting that linked selection or genetic draft are more important than conventional genetic drift. Draft is most severe in asexual populations, for which models predict that the fitness differences rather than the population size determine the level of neutral diversity. As outcrossing becomes more frequent, the strength of draft decreases and diversity increases. With increasing coalescence times, selection becomes more efficient as there is more time to differentiate deleterious from beneficial alleles. In obligately sexual populations, most interference is restricted to tightly linked loci and the number of sweeps per map length and generation determines genetic diversity.

Since interference slows adaptation, one expects that adaptation can select for higher recombination rates (Charlesworth, 1993). Indeed, positive selection results in indirect selection on recombination modifiers (Barton, 1995a; Barton and Otto, 2005; Hartfield *et al.*, 2010; Otto and Barton, 1997). Changing frequencies of outcrossing have been observed in evolution experiments (Becks and Agrawal, 2010). However, the evolution of recombination and outcrossing rates in rapidly adapting populations remains poorly understood, both theoretically and empirically.

The traveling wave models discussed above assume a large number of polymorphisms with similar effects on fitness and a smooth fitness distribution, which are drastic idealizations. More typically, one finds a handful of polymorphisms with a distribution of effects (Barrick *et al.*, 2009; Lang *et al.*, 2011; Strelkowa and Lässig, 2012). Simulations indicate, however, that statistical properties of genealogies are rather robust regarding model assumptions as long as draft dominates over drift (Neher and Hallatschek, 2013). Appropriate genealogical models are prerequisite for demographic inference. If, for example, a neutral coalescent model is used to infer the population size history of a rapidly adapting population, one would conclude that the population has been expanding. Incidentally, this is inferred in most cases. Some progress towards incorporating the effect of purifying selection into estimates from reconstructed genealogies has been made recently (Nicolaisen and Desai, 2012; O'Fallon, 2011). Alternative genealogical models accounting for selection should be included into popular analysis programs such as BEAST (Drummond and Rambaut, 2007).

It is still common to assign an "effective" size, N_e, to various populations. In most cases, N_e is a proxy for genetic diversity, which depends on the time to the most recent common ancestor. With the realization that coalescence times depend on linked selection and genetic draft, rather than the population size and genetic drift, the term should be avoided and replaced by T_c, the time scale of coalescence. Defining N_e suggests that the neutral model is valid as long as N_e is used instead of N. We have seen multiple times that drift and draft are of rather different natures and that this difference cannot be captured by a simple rescaling. Each quantity then requires its own private N_e, rendering the concept essentially useless. Some quantities like site frequency spectra are qualitatively different and no N_e maps them to a neutral model. The (census) population size is nevertheless important in discovering beneficial mutations. For this reason, large populations are expect to respond more quickly to environmental change as we are painfully aware in the case of antibiotic resistance of pathogens. Large populations might therefore track phenotypic optima more closely resulting in beneficial mutations with smaller effect, which in turn might explain their greater diversity.

The majority of models discussed assume a time invariant fitness landscape. This assumption reflects our ignorance regarding the degree and timescale of environmental fluctuations (for work on selection in time-dependent fitness landscapes, see Mustonen and Lässig (2009)). Time-variable selection pressures, combined with spatial variation,

could potentially have strong effects. Similarly, frequency-dependent selection and more generally the interaction of evolution with ecology are important avenues for future work. The challenge consists of choosing useful models that are tractable, appropriate, and predictive.

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Appendix A: Glossary

- Genetic drift: stochastic changes in allele frequencies due to non-heritable variation in offspring number.
- Purifying selection: selection against deleterious mutations.
- Positive selection : selection for novel beneficial mutations.
- Genetic draft: changes in allele frequencies due to (partly) heritable random associations with genetic backgrounds.
- Hitchhiking: rapid rise in frequency through an association with a very fit background.
- Selective interference: reduction of fixation probability through competition with other beneficial alleles.
- Clonal interference: competition between well adapted asexual subpopulations from which only one subpopulation emerges as winner.
- Branching process: stochastic model of reproducing and dying individuals without a constraint on the overall population size.
- Epistasis: background dependence of the effect of mutations. Epistasis can result in rugged fitness landscapes.
- Kingman coalescent: basic coalescence process where random pairs of individuals merge.
- Multiple merger coalescent: coalescent process with simultaneous merging of more than 2 lineages.
- Bolthausen-Sznitman Coalescent (BSC): special multiple merger coalescent which approximates genealogies in many models of adaptation.